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(71) Applicant *(for all designated States except AT, US)*: NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: NOZULAK, Joachim [DE/DE]; In der Ziegelei 1, 79423 Heitersheim (DE).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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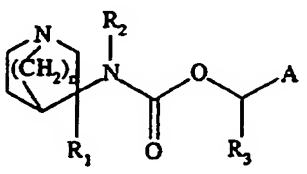
(54) Title: AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS



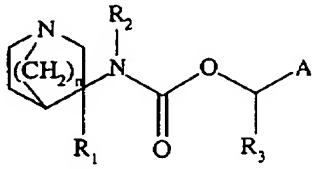
(I)

(57) Abstract: The invention provides compounds of formula (I) wherein n, A, R_1, R_2 and R_3 are as defined in the description, and the preparation thereof. The compounds of formula (I) are useful as pharmaceuticals.

AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

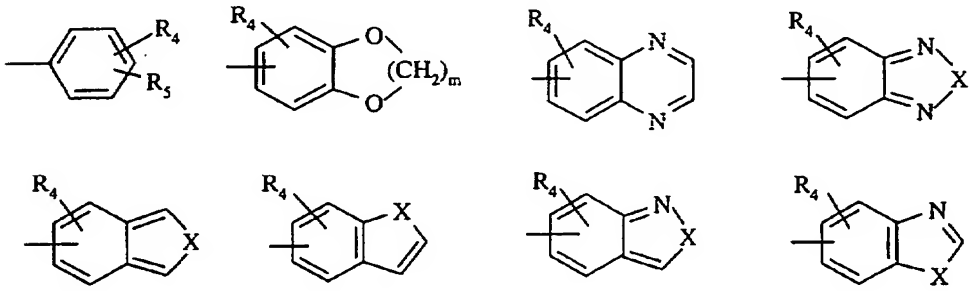
The present invention relates to novel azabicyclic carbamates, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



I

wherein n is 1 or 2, R_1, R_2 and R_3, independently, are hydrogen or (C_{1-4})alkyl and A is a group of formula



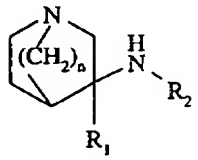
wherein m is 1, 2 or 3, X is O, S, NH or CH_2 and R_4 and R_5, independently, are hydrogen, halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino, nitro, trifluoromethyl or phenyl, in free base or acid addition salt form.

Halogen denotes fluorine, bromine, chlorine or iodine.

Any alkyl, alkoxy and alkylthio groups are branched or straight chain groups. They are preferably methyl, methoxy or methylthio groups.

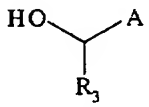
On account of the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the step of reacting a compound of formula II



II

wherein n, R_1 and R_2 are as defined above, with a compound of formula III

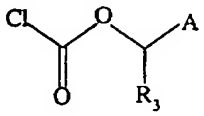


III

wherein R_3 and A are as defined above, and N, N'-carbonyldiimidazole or di(N-succinimidyl)carbonate, and recovering the resulting compound of formula I in free base or acid addition salt form.

According to a preferred embodiment, in a first step the compound of formula III is reacted with N, N'-carbonyldiimidazole, and the resulting compound is reacted with the compound of formula II.

Alternatively, the compound of formula II can be reacted with a compound of formula IV



IV

wherein R_3 and A are as defined above.

The reactions can be effected according to conventional methods, e.g. as described in the examples.

Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice versa.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures. Alternatively, optically pure starting materials can be used.

The starting materials of formula II, III and IV are known or may be obtained from known compounds, using conventional procedures.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (nAChR) agonists.

In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at human α7 nAChR is carried out with a rat pituitary cell line stably expressing the human α7 nAChR. As a read out, the calcium influx upon stimulation of the receptor is used. In this assay, agents of the invention exhibit pEC_{50} values of about 5 to about 8.

b) To assess the activity of the agents of the invention on the human neuronal nAChR α4β2, a similar functional assay is carried out using a human epithelial cell line stable expressing the human α4β2 subtype. In this assay, agents of the invention show selectivity for the α7 nAChR subtypes.

c) To assess the activity of the compounds of the invention on the "ganglionic subtype" and the muscle type of nicotinic receptor, similar functional assays as described under a) are carried out with a human epithelial cell line stably

expressing the human ganglionic subtype or a cell line endogenously expressing the human muscle type of nicotinic receptors. In these assays, agents of the invention display no or little activity on the ganglionic and muscle type of nicotinic receptor subtypes.

In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the agents of the invention induce significant sensory gating at concentrations of about 10 to about 40 μM.

The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia, mania, depression and anxiety, and for the treatment of neurodegenerative disorders such as senile dementia, Alzheimer's disease and other intellectual impairment disorders, such as attention deficit hyperactivity disorders (ADHD); Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis. The usefulness of α7 nAChR agonists in neurodegeneration is documented in the literature, e.g. in Wang et al., J. biol. Chem. 275, 5626-5632 (2000).

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 100, preferably from about 0.1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 5 to about 300 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The preferred compound is the stereoisomer of the (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester, the succinate of which has a melting

point of 83-84°C and which has an optical rotation of +14.6° (c=1; water, 20°C, 589 nm), which is the compound of Example 61.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of any condition mentioned above.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from about 1 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Example 1 : (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-phenyl-ethyl ester

Imidazole-1-carboxylic acid 1-phenyl-ethyl ester

To a solution of DL-1-phenylethanol 1.21 ml (10.0 mmol) in 10ml tetrahydrofurane, N,N'-carbonyldiimidazole 1.70 g (10.5 mmol) is added. The white suspension is heated up to 50°C and stirred for 40 minutes at this temperature. The reaction mixture is cooled and evaporated. The crude product is purified by flash chromatography (hexane / ethyl acetate 80 / 20) to yield the title product as colorless oil.

(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-phenyl-ethyl ester

To a solution of imidazole-1-carboxylic acid 1-phenyl-ethyl ester 0.50 g (2.31 mmol) in 5 ml dimethylformamide, 3-aminoquinuclidine dihydrochloride 0.46 g (2.31 mmol) and sodium carbonate 0.49 g (4.62 mmol) are added. The suspension is heated up to 80 °C and stirred for 18 hours at this temperature. The reaction mixture is then cooled and extracted with water and ethylacetate. The combined organic phases are dried and evaporated. The oily residue is dried, dissolved in ether and acidified with a 4 M hydrochloric acid dioxane solution. The precipitating crystals are filtered, washed with ether and dried to give the title product. Mp = 71 - 72 °C (decomposition).

Example 2: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

3-Aminoquinuclidine dihydrochloride 996 mg (5.0 mmol) is added slowly to a stirred suspension of 676 mg (15.5 mmol) sodium hydride (dispersion 55%) in dimethylformamide (15 ml). Thereafter the suspension is stirred for another 90 minutes at room temperature and then carbobenzoxy chloride 0.72 ml (5.1 mmol) is added slowly. After another two hours at room temperature, the suspension is quenched by carefully adding water. The solvent is then evaporated at 70 °C / 16 mbar. The residue is taken up in water and ethyl acetate. The organic phase is separated and the water phase two-times re-extracted with ethyl acetate. The combined organic phase is dried and evaporated to give the crude oily product which is taken up in dioxane and 0.72 ml of a 4M hydrochloric acid is added. The precipitating product is recrystallised from dioxane/ether to give the hydrochloride of the title product. Mp=192 - 193 °C.

Example 3 : (R)-(+)-(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

Sodium hydride (dispersion 55%) 0.33 g (7.5 mmol) is washed with petrolether and the solvent is removed by separation (decantation). Then, the sodium hydride is carefully suspended in dimethylformamide (12.5 ml). To this suspension (R)-(+)-3-aminoquinuclidine dihydrochloride 0.50 g (2.5 mmol) is added. The initially exothermic reaction is then stirred at room temperature for one hour and then carbobenzoxy chloride 0.39 ml (2.75 mmol) is added to the reaction mixture within 15 minutes. The again initially exothermic reaction is stirred at room temperature for 90 minutes, then the mixture is poured into 10% brine (NaCl/water solution) and then four-times extracted with toluene. The combined organic phases are dried and evaporated. The crude oily residue is dissolved in dioxane (5 ml) and 0.31 ml of a 4 M hydrochloric acid is added. The mixture is then stirred at room temperature till the product precipitates. The crystals are filtered, washed with dioxane and ether and dried to give the title product. Mp = 228 – 229 °C. Optical rotation +6.3 ° (c=0.5, water).

Example 4: (S)-(-)-(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

Sodium hydride (dispersion 55%) 0.33 g (7.5 mmol) is washed with petrolether and the solvent is removed by separation (decantation). Then, the sodium hydride is carefully suspended in dimethylformamide (12.5 ml). To this suspension (S)-(-)-3-aminoquinuclidine dihydrochloride 0.50 g (2.5 mmol) is added. The initially exothermic reaction is then stirred at room temperature for one hour and then carbobenzoxy chloride 0.39 ml (2.75 mmol) is added to the reaction mixture within 15 minutes. The again initially exothermic reaction is stirred at room temperature for 90 minutes then the mixture is poured into 10% brine (NaCl/water solution) and then four-times extracted with toluene. The combined organic phases are dried and evaporated. The crude oily residue is dissolved in dioxane (5 ml) and 0.31 ml of a 4 M hydrochloric acid is added. The mixture is then stirred at room temperature till the product precipitates. The crystals are filtered, washed with dioxane and ether and dried to give the title product. Mp = 221 – 223 °C. Optical rotation –8.0 ° (c=0.5, water).

Example 5: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 4-butyl-benzyl ester

Triethylamine 1.05 ml (7.5 mmol) and 0.80 g di-(N-succinimidyl)carbonate are added to a solution of (4-butyl-phenyl)methanol 0.47 ml (2.75 mmol) in 15 ml dichloromethane. The initial suspension is stirred at room temperature for 45 minutes to become a clear solution. This mixture is added dropwise to a solution of 3-aminoquinuclidine 0.32 g (2.5 mmol) and 0.52 ml (1.5 mmol) triethylamine in 10 ml dichloromethane. The reaction mixture is subsequently stirred for another two hours at room temperature. Afterwards the mixture is washed with 20 ml water. The organic phase is separated, dried and evaporated. The crude product is dissolved in 5 ml dichloromethane and acidified with a saturated solution of hydrochloric acid in ether. By addition of 50 ml ether a white product precipitates. The crystals are filtered, washed with ether and dried to give the title product. Mp = 174 - 175°C (decomposition).

The following compounds of formula I wherein n is 2, R_1 and R_2 are hydrogen and A is a substituted phenyl group can be prepared in analogy to Examples 1, 2 or 5.

Example	R_3	R_4	R_5	Mp / Optical Rotation
6	H	o-OMe	H	89-90°C (hydrochloride)
7	H	2-OMe	3-OMe	93-95°C (hydrochloride)
8	H	p-phenyl	H	193-195°C (hydrochloride)
9	H	o-Br	H	203-204°C (hydrochloride)
10	H	o-NO_2	H	177-178°C (hydrochloride)
11	H	p-NO_2	H	89-90°C (hydrochloride)
12	H	2-OMe	5-Br	147-149°C (hydrochloride)
13	H	m-phenoxy	H	82-83°C (hydrochloride)
14	H	o-Cl	H	82-83°C (hydrochloride)
15	H	3-NO_2	5-NO_2	93-94°C (hydrochloride)
16	H	3-Cl	4-Cl	*
17	H	m-OMe	H	139-140°C (hydrochloride)
18	H	3-NO_2	4-Me	86-88°C (hydrochloride)
19	H	3-Me	5-Me	183-184°C (hydrochloride)
20	H	p-CF_3	H	143-144°C (hydrochloride)
21	H	o-Me	H	174-176°C (hydrochloride)
22	H	p-Me	H	194-196°C (hydrochloride)
23	H	p-isopropyl	H	235°C (hydrochloride)
24	Me	p-Me	H	168-170°C (hydrochloride)

25 cis/trans racemic mixture	Me	H	H	71-72 °C (hydrochloride)
26 Stereoisomer-1	Me	H	H	182-184 °C (hydrochloride) ; optical rotation: + 32.4 ° (c=1; water, 24 °C, 589 nm)
27 Stereoisomer-2	Me	H	H	151-152 °C (succinate) optical rotation: - 9.7 ° (c=1; methanol, 22 °C, 589 nm)
28 Stereoisomer-3	Me	H	H	optical rotation: + 12.5 ° (c=1; methanol, 20 °C, 589 nm)
29 Stereoisomer-4	Me	H	H	117-119 °C (fumarate) optical rotation: - 25.0 ° (c=1; methanol, 20 °C, 589 nm)
30	H	3-OMe	5-OMe	179-180 °C (hydrochloride)
31	H	3-Me	4-NO_2	165-167 °C (hydrochloride)
32	Me	2-Cl	4-Cl	212-214 °C (hydrochloride)
33	H	p-Ethyl	H	208-209 °C (hydrochloride)
34	H	p-Br	H	190-191 °C (hydrochloride)
35	H	3-CF_3	5-CF_3	157-158 °C (hydrochloride)
36	H	p-SMe	H	164-166 °C (hydrochloride)
37	H	2-NO_2	5-Me	198-199 °C (hydrochloride)
38	H	3-OMe	4-OMe	221-223 °C (hydrochloride)
39	H	2-Cl	6-Cl	251-252 °C (hydrochloride)
40	H	p-CO_2Me	H	220-222 °C (hydrochloride)
41	Me	p-tButyl	H	232-233 °C (hydrochloride)
42	Ethyl	H	H	**
43	Me	p-Cl	H	132-135 °C (hydrochloride)
44	Me	o-Me	H	219-220 °C (hydrochloride)
45	Me	p-Br	H	163-165 °C (hydrochloride)
46	Me	3-Cl	4-Cl	240-241 °C (hydrochloride)
47	Me	p-F	H	219-220 °C (hydrochloride)
48	H	m-Br	H	186-187 °C (hydrochloride)
49	H	m-Me	H	174-175 °C (hydrochloride)
50	H	m-OBenzyl	H	168-169 °C (hydrochloride)
51	H	2-Cl	5-Cl	205-207 °C (hydrochloride)
52	H	2-OMe	5-OMe	162-163 °C (hydrochloride)
53	H	2-NO_2	4-Cl	204-205 °C (hydrochloride)
54 cis/trans racemic mixture	Me	o-Cl	H	230-232 °C (hydrochloride)

55 Stereoisomer-1	Me	o-Cl	H	229-230 °C (hydrochloride) optical rotation: - 8.6 ° (c=1; water, 20 °C, 589 nm)
56 Stereoisomer-2	Me	o-Cl	H	255-257 °C (hydrochloride) optical rotation: + 26.8 ° (c=1; water, 22 °C, 589 nm)
57 Stereoisomer-3	Me	o-Cl	H	229-230 °C (hydrochloride) optical rotation: + 8.9 ° (c=1; water, 20 °C, 589 nm)
58 Stereoisomer-4	Me	o-Cl	H	257-258 °C (hydrochloride) optical rotation: - 30.9 ° (c=1; water, 22 °C, 589 nm)
59 Stereoisomer-1	Me	o-F	H	83-84 °C (succinate) optical rotation: + 15.4 ° (c=1; water, 20 °C, 589 nm)
60 Stereoisomer-2	Me	o-F	H	146-147 °C (succinate) optical rotation: + 2.5 ° (c=1; water, 20 °C, 589 nm)
61 Stereoisomer-3	Me	o-F	H	83-84 °C (succinate) optical rotation: + 14.6 ° (c=1; water, 20 °C, 589 nm)
62 Stereoisomer-4	Me	o-F	H	136-137 °C (succinate) optical rotation: - 4.8 ° (c=1; water, 20 °C, 589 nm)

Me = Methyl

* IS: Carbonyl absorption at 1695 cm^{-1}

* * IS: Carbonyl absorption at 1712 cm^{-1}

Example 63: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,3]dioxol-5-ylmethyl ester

Prepared in analogy to example 1, 2 or 5.

Mp (hydrochloride) = 186-187°C.

Example 64: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,3]dioxol-4-nitro-5-ylmethyl ester

Prepared in analogy to example 1, 2 or 5.

Mp (hydrochloride) = 216-218 °C.

Example 65: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 3,4,5-trimethoxy-benzyl ester

Prepared in analogy to example 1, 2 or 5.

Mp (hydrochloride) = 211-212 °C.

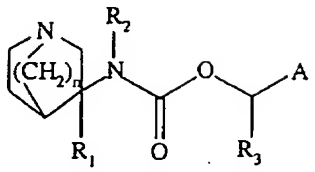
Example 66 **1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,2,5]thiadiazol-5-ylmethyl ester**

Prepared in analogy to example 1, 2 or 5.

IS: Carbonyl absorption at 1718 cm^{-1}

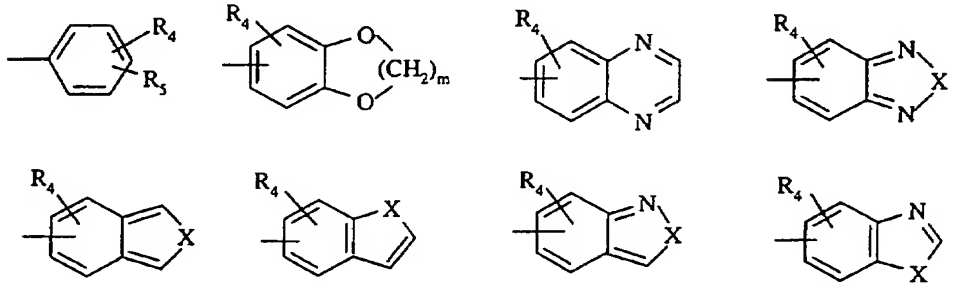
Claims:

1. A compound of formula I



I

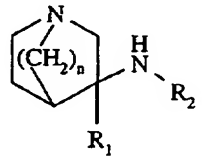
wherein n is 1 or 2, R_1, R_2 and R_3, independently, are hydrogen or (C_{1-4})alkyl and A is a group of formula



wherein m is 1, 2 or 3, X is O, S, NH or CH_2 and R_4 and R_5, independently, are hydrogen, halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino, nitro, trifluoromethyl or phenyl, in free base or acid addition salt form.

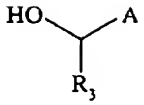
2. A compound according to claim 1 which is the stereoisomer of the (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester, the succinate of which has a melting point of 83-84°C and which has an optical rotation of +14.6° (c=1; water, 20°C, 589 nm), in free base or acid addition salt form.

3. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

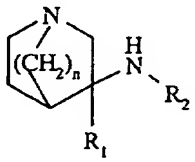
wherein n, R_1 and R_2 are as defined in claim 1, with a compound of formula III



III

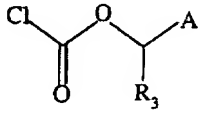
wherein R_3 and A are as defined in claim 1, and N, N'-carbonyldiimidazole or di(N-succinimidyl)carbonate, and recovering the resulting compound of formula I in free base or acid addition salt form.

4. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

wherein n, R_1 and R_2 are as defined in claim 1, with a compound of formula IV



IV

wherein R_3 and A are as defined above, and recovering the resulting compound of formula I in free base or acid addition salt form.

5. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

6. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic and neurodegenerative disorders.

7. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

8. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of psychotic and neurodegenerative disorders.

9. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic and neurodegenerative disorders.

10. A method for the treatment of psychotic and neurodegenerative disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

INTERNATIONAL SEARCH REPORT

Intern .ial Application No
PCT/EP 01/05008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D453/06 A61K31/439 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 988 429 A (JOHN MACOR ET AL.) 23 November 1999 (1999-11-23) column 7 -column 8; claims	1,7,8
A	WO 96 08468 A (H. LUNDBECK A/S) 21 March 1996 (1996-03-21) claims	1,7,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2001	22/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern nal Application No
PCT/EP 01/05008

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5988429	A	23-11-1999	NONE		
WO 9608468	A	21-03-1996	AU	3470495 A	29-03-1996
			WO	9608468 A1	21-03-1996
			ZA	9507746 A	25-07-1996